

prejudice, claims 63, 65, 68, 69, 70, 71, 77, and 78 are amended, and new claims 79-102 are added, to more particularly point out and distinctly claim the invention, and according to the suggestions of Examiner Katharine Davis made during the phone conferences with Eileen Falvey, representative of Applicant, on January 11, 2002 and January 15, 2002.

The specification has been amended to remove the Table of Contents and the web site addresses. A marked-up version of the amendments to the specification is attached hereto as Exhibit A, which indicates added matter by underlining and deleted matter by brackets.

New claims 79, 80, and 81 claim subject matter similar to that of now canceled claim 52, and are supported in the specification at page 73, line 16-22; page 74 lines 5-12; and page 75, line 7 to page 79, line 19. New claims 82-85 claim subject matter similar to that of now canceled claim 61 and 62, and are supported in the specification at page 73, line 16-22; page 74 lines 5-12; and page 75, line 7 to page 79, line 19. New dependent claims 86-100 claim subject matter similar to claims 63, 65, 68, 69, 70, 71, 77, and 78, but are dependent on the newly added claims 79-85. These amendments and new claims are fully supported by the instant specification (see, *e.g.*, page 12, lines 19 to 28; page 72 line 1, page 78, line 29 to page 79, line 2; and, in general, Section 5.8), and, as such, do not represent new subject matter. A marked-up version of the claim amendments are attached hereto as Exhibit B, which indicates added matter by underlining and deleted matter by brackets.

Thus, claims 51, 55-60, 63-73, and 77-102 will be pending upon entry of the instant amendments. A copy of the pending claims upon entry of the amendments is attached hereto as Exhibit C. Applicant respectfully requests that the amendments and remarks presented herein be entered into the record of the instant application.

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Entry of the foregoing amendments and remarks is respectfully requested. If any outstanding issues remain, Applicant respectfully requests that the Examiner call the undersigned to discuss such issues.

Respectfully submitted,

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Enclosures

EXHIBIT A
(MARKED-UP VERSION OF THE AMENDMENTS TO THE
SPECIFICATION)

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EXHIBIT A:
MARKED-UP VERSION OF THE AMENDMENTS TO THE SPECIFICATION
(indicating deletions by bracketing)
Application No. 09/411,075 Atty. Docket No. 8449-054-999

IN THE SPECIFICATION:

Amend the paragraph beginning "Protein "spots"" which spans pages 32 and 33 as follows:

"Protein spots" that appear in samples from HSPR-positive membranes but are absent in samples from HSPR-negative membrane proteins can be analyzed further. Differences can be detected by visual inspection of gels, or by using densitometry and computerized image analysis thereby facilitating spot detection, background subtraction and spot matching (see Pennigton et al., 1997, Trends Cell Biol. 7: 168-73). Further, HSPR protein can be detected by Western Blot analysis of 2D gels, if HSPR antibody is available (Harlow and Lane, *supra*). Once identified, the molecular weight (M_r) and the isoelectric point (pI) of an HSPR-positive cell specific protein can be determined by calibrating its position relative to known standards run in parallel on 2D gels. Specific proteins can then be purified, and their sequence determined by Edman degradation sequencing (Edman and Begg, 1967, Eur. J. Biochem. 1:80-91), automated by electroblotting onto polyvinylidene difluoride (PVDF) membranes using Edman degradation chemistry determined by gas-liquid phase, liquid-pulse or solid phase sequence analysis (Findlay and Geisow, 1989, Protein Sequencing: A Practical Approach, IRL Press, Oxford, pp. 1-199). Alternatively, proteins and peptides can be characterized by mass spectrometry, using peptide-mass fingerprinting or protein sequencing methodologies to identify sequence information and post-translational modifications (Dainese et al., 1997, Electrophoresis, 18:432-42; Mann and Wilm, 1995, Trends

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Biochem. Sci., 20:219-24; Yates, 1996, Methods Enzymol. 271:351-77). After limited sequence information is obtained, protein (Swiss-Prot[; <http://www.expasy.ch>]) and nucleic acid sequence (Genbank and EMBL[; <http://ncbi.nlm.nih.gov>]) databases can be searched to determine if protein sequence is novel. Novel proteins will be analyzed further in HSP binding assays, used to generate antibodies, as described in Section 5.4, and used for identification of HSPR nucleic acid sequences.

Amend the paragraph beginning "In a preferred embodiment" which spans pages 44 and 45 as follows:

In a preferred embodiment, mRNA from HSPR positive is compared to mRNA from HSPR negative cells by differential display. HSPR positive cells and HSPR negative cells are prepared as described in Section 5.1, *supra*. The preparation of mRNA is as described in Section 5.5.1. Following RT-PCR using the specific set of primers described hereinabove, RT-PCR products are displayed on thin polyacrylamide gels containing 8% urea, the type used for DNA sequencing analysis. Products that are detected in HSPR positive cells but absent in HSPR negative control cells are chosen to be analyzed further. Gel purification and sequence analysis of such products can be performed to identify HSPR nucleic acid candidates. Protein-coding sequences of HSPR candidates, i.e., sequences present in HSPR positive cells but not in control cells, can be compared to known protein sequences in a data base such as Swiss-prot (Bairoch & Apweiler, 1998, Nucl. Acids Res. 26:38-42[; <http://www.expasy.ch>]). Novel sequences can be chosen as potential HSPR candidates. Such gene products can then be isolated from the cDNA population using standard cloning techniques (Ausubel et al., 1992, *supra*), and can be tested for their ability to bind HSP ligand and antibodies.

EXHIBIT B
(MARKED-UP VERSION OF THE CLAIM AMENDMENTS)

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EXHIBIT B:
MARKED-UP VERSION OF THE CLAIM AMENDMENTS
(indicating additions by underlining and deletions by bracketing)
Application No. 09/411,075 Atty. Docket No. 8449-054-999

63. (Amended) The method of claim 51 [or 52] wherein the molecule is a peptide or protein, or derivative, analog or fragment thereof.
65. (Amended) The method of claim 51 [or 52] wherein the molecule is a small organic molecule, a nonpeptide, or an antibody.
68. (Amended) The method of claim 51 [or 52] wherein the molecule is attached to a solid surface.
69. (Amended) A method for identifying a molecule useful for the treatment of cancer comprising carrying out the method of claim 51, further comprising the step of administering the molecule to a non-human animal having a tumor, and determining whether the molecule alters tumor progression in the [treated] non-human animal.
70. (Amended) A method for identifying a molecule useful for the treatment of an infectious disease comprising carrying out the method of claim 51, further comprising the step of administering the molecule to a non-human animal infected with a pathogen, and determining whether the molecule ameliorates the infectious disease in the [treated] non-human animal.
71. (Amended) A method for identifying a molecule useful for the treatment of an autoimmune disease comprising carrying out the method of claim 51, further comprising the step of administering the molecule to a non-human animal suffering from an autoimmune disease, and determining whether the molecule ameliorates the autoimmune disease in the [treated] non-human animal.

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77. (Amended) The method of claim 51, [52,] 69, 70, 71, [74, 75, or 76,] wherein the heat shock protein receptor is selected from the group consisting of an Hsp70 receptor, an Hsp 90 receptor, and a gp96 receptor.

78. (Amended) The method of claim 51, [52,] 69, 70, 71, [74, 75, or 76,] wherein the heat shock protein receptor positive cells are purified from heat shock protein receptor negative cells.

EXHIBIT C
(PENDING CLAIMS)

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**EXHIBIT C:
PENDING CLAIMS**

Application No. 09/411,075 Atty. Docket No. 8449-054-999
(as amended February 1, 2002)

51. A method for screening a molecule for the ability to modulate heat shock protein receptor activity comprising:

- (a) contacting heat shock receptor positive cells with the molecule; and
- (b) comparing the level of heat shock protein receptor binding activity in the heat shock receptor positive cells contacted with the molecule to the amount of heat shock protein receptor binding activity in the heat shock receptor positive cells not so contacted,

wherein an increase or decrease in the amount of heat shock protein receptor binding activity in the contacted heat shock receptor positive cells relative to the amount of heat shock protein receptor binding activity in the heat shock receptor positive cells not so contacted indicates that the molecule has the ability to modulate heat shock protein receptor activity.

55. The method of claim 51 wherein the level of heat shock protein receptor binding activity is assayed by measuring the ability of the molecule to bind to the heat shock protein receptor positive cells.

56. The method of claim 51 wherein the level of heat shock protein receptor binding activity is assayed by measuring the ability of the molecule to modulate the binding of a heat shock protein or a heat shock protein-peptide complex to the cells.

57. The method of claim 56 wherein the molecule increases the binding of the heat shock protein or the heat shock protein-peptide complex to the cells.

58. The method of claim 56 wherein the molecule decreases the binding of the heat shock protein or the heat shock protein-peptide complex to the cells.

59. The method of any one of claims 56 to 58 wherein the heat shock protein is an Hsp70, an Hsp 90, or gp96.

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60. The method of claim 51 wherein the heat shock protein receptor binding activity is the ability to interact with a heat shock protein receptor antibody.

63. The method of claim 51 wherein the molecule is a peptide or protein, or derivative, analog or fragment thereof.

64. The method of claim 63 wherein the peptide is a member of a peptide library.

65. The method of claim 51 wherein the molecule is a small organic molecule, a nonpeptide, or an antibody.

66. The method of claim 65 wherein the nonpeptide is a member of a nonpeptide library.

67. The method of claim 66 wherein the small organic molecule is a member of a small molecule library.

68. The method of claim 51 wherein the molecule is attached to a solid surface.

69. A method for identifying a molecule useful for the treatment of cancer comprising carrying out the method of claim 51, further comprising the step of administering the molecule to a non-human animal having a tumor, and determining whether the molecule alters tumor progression in the non-human animal.

70. A method for identifying a molecule useful for the treatment of an infectious disease comprising carrying out the method of claim 51, further comprising the step of administering the molecule to a non-human animal infected with a pathogen, and determining whether the molecule ameliorates the infectious disease in the non-human animal.

71. A method for identifying a molecule useful for the treatment of an autoimmune disease comprising carrying out the method of claim 51, further comprising the step of administering the molecule to a non-human animal suffering from an autoimmune disease,

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and determining whether the molecule ameliorates the autoimmune disease in the non-human animal.

77. The method of claim 51, 69, 70, 71, wherein the heat shock protein receptor is selected from the group consisting of an Hsp70 receptor, an Hsp 90 receptor, and a gp96 receptor.

78. The method of claim 51, 69, 70, 71, wherein the heat shock protein receptor positive cells are purified from heat shock protein receptor negative cells.

79. A method for screening a plurality of molecules for one or more molecule(s) having the ability to modulate, directly or indirectly, the ability of heat shock receptor positive cells to stimulate the activation of cytotoxic T cells *in vitro* comprising:

- (a) adding said plurality of molecules to a mixture of heat shock protein receptor positive cells and cytotoxic T cells under conditions conducive to the activation of cytotoxic T cells; and
- (b) comparing antigenic cell cytotoxicity of said T cells with the cytotoxicity of T cells that are formed in the absence of said plurality of molecules,

wherein a lower or higher degree of cytotoxicity indicates that one or more molecules in said plurality of molecules modulates the activation of cytotoxic T cells.

80. A method for screening a molecule for the ability to modulate, directly or indirectly, the ability of heat shock receptor positive cells to stimulate the activation of cytotoxic T cells *in vitro* comprising:

- (a) adding the molecule to a mixture comprising (i) purified heat shock protein receptor positive cells and (ii) cytotoxic T cells, under conditions conducive to the activation of cytotoxic T cells; and
- (b) comparing antigenic cell cytotoxicity of said T cells with the cytotoxicity of T cells that are formed in the absence of said molecule,

wherein a lower or higher degree of cytotoxicity indicates that the molecule modulates the activation of cytotoxic T cells.

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81. A method for screening an antibody specific to a heat shock protein or a heat shock protein receptor for the ability to modulate, directly or indirectly, the ability of heat shock receptor positive cells to stimulate the activation of cytotoxic T cells *in vitro* comprising:

- (a) adding the antibody to a mixture of heat shock protein receptor positive cells and cytotoxic T cells under conditions conducive to the activation of cytotoxic T cells; and
- (b) comparing antigenic cell cytotoxicity of said T cells with the cytotoxicity of T cells that are formed in the absence of said antibody,

wherein a lower or higher degree of cytotoxicity indicates that the antibody modulates the activation of cytotoxic T cells.

82. A method for screening a plurality of molecules for one or more molecule(s) having the ability to modulate, directly or indirectly, antigen presentation activity of heat shock receptor positive cells comprising:

- (a) adding said plurality of molecules to heat shock protein receptor positive cells;
- (b) measuring antigen presentation by said heat shock protein receptor positive cells in the presence of said plurality of molecules; and
- (c) comparing antigen presentation activity by the heat shock receptor positive cells in the presence of said plurality of molecules with the antigen presentation activity by the heat shock receptor positive cells in the absence of said plurality of molecules,

wherein a lower or higher degree of antigen presentation indicates that one or more molecule(s) modulates the antigen presentation activity of the heat shock receptor positive cells.

83. A method for screening an antibody specific to a heat shock protein or a heat shock protein receptor for the ability to modulate, directly or indirectly, antigen presentation activity of heat shock receptor positive cells comprising:

- (a) adding an antibody specific to a heat shock protein or a heat shock protein receptor to heat shock protein receptor positive cells;

- (b) measuring antigen presentation by said heat shock protein receptor positive cells in the presence of said antibody; and
- (c) comparing antigen presentation activity by the heat shock receptor positive cells in the presence of the antibody with the antigen presentation activity by the heat shock receptor positive cells in the absence of the antibody,

wherein a lower or higher degree of antigen presentation indicates that the antibody modulates the antigen presentation activity of the heat shock receptor positive cells.

84. A method for screening a molecule for the ability to modulate, directly or indirectly, antigen presentation activity of heat shock receptor positive cells comprising:

- (a) adding a molecule to purified heat shock protein receptor positive cells;
- (b) measuring antigen presentation by said heat shock protein receptor positive cells in the presence of said molecule; and
- (c) comparing the antigen presentation activity by the purified heat shock receptor positive cells in the presence of the molecule with the antigen presentation activity by the purified heat shock receptor positive cells in the absence of the molecule,

wherein a lower or higher degree of antigen presentation indicates that the molecule modulates the antigen presentation activity of the heat shock receptor positive cells.

85. The method of claim 82, 83, or 84, wherein measuring antigen presentation is carried out by measuring representation of a peptide by an MHC molecule.

86. The method of claim 79, 81, 82, or 84, wherein the molecule is a peptide or protein, or derivative, analog or fragment thereof.

87. The method of claim 79, 81, 82, or 84, wherein the molecule is a small organic molecule or a nonpeptide.

88. The method of claim 87, wherein the nonpeptide is a member of a nonpeptide library.

89. The method of claim 87, wherein the small organic molecule is a member of a small molecule library.
90. The method of claim 79, 81, 82, or 84, wherein the molecule is attached to a solid surface.
91. The method of claim 80 or 83, wherein the antibody is attached to a solid surface.
92. The method of claim 79, 80, 81, 82, 83, or 84, wherein the heat shock protein receptor positive cells are macrophage or dendritic cells.
93. A method for identifying a molecule useful for the treatment of cancer comprising carrying out the method of claim 79, 81, 82, or 84, further comprising the step of administering the molecule to a non-human animal having a tumor, and determining whether the molecule alters tumor progression in the non-human animal.
94. A method for identifying an antibody useful for the treatment of cancer comprising carrying out the method of claim 80 or 83, further comprising the step of administering the antibody to a non-human animal having a tumor, and determining whether the antibody alters tumor progression in the non-human animal.
95. A method for identifying a molecule useful for the treatment of an infectious disease comprising carrying out the method of claim 79, 81, 82, or 84, further comprising the step of administering the molecule to a non-human animal infected with a pathogen, and determining whether the molecule ameliorates the infectious disease in the non-human animal.
96. A method for identifying an antibody useful for the treatment of an infectious disease comprising carrying out the method of claim 80 or 83, further comprising the step of administering the antibody to a non-human animal infected with a pathogen, and determining whether the antibody ameliorates the infectious disease in the non-human animal.

97. A method for identifying a molecule useful for the treatment of an autoimmune disease comprising carrying out the method of claim 79, 81, 82, or 84, further comprising the step of administering the molecule to a non-human animal suffering from an autoimmune disease, and determining whether the molecule ameliorates the autoimmune disease in the non-human animal.

98. A method for identifying an antibody useful for the treatment of an autoimmune disease comprising carrying out the method of claim 80 or 83, further comprising the step of administering the antibody to a non-human animal suffering from an autoimmune disease, and determining whether the antibody ameliorates the autoimmune disease in the non-human animal.

99. The method of claim 79, 80, 81, 82, 83, or 84, wherein the heat shock protein receptor is selected from the group consisting of an Hsp70 receptor, an Hsp 90 receptor, and a gp96 receptor.

100. The method of claim 79, 80, 81, 82, 83, or 84, wherein the heat shock protein receptor positive cells are purified from heat shock protein receptor negative cells.

101. The method of claim 79, 81, 82, or 84, wherein the molecule is purified.

102. The method of claim 80 or 83, wherein the antibody is purified.